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Midterm Technical Report

LASER IRRADIATION EFFECTS: A FUNCTIONAL ASSESSMENT

David O. Robbins, Ph.D.

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Specification of damage criteria and establishment of morphological data resulting from laser exposure has been an important mission for biomedical researchers and strategic planners. Equally important, however, from a military standpoint is the impact that this alteration, whether temporary or permanent, has on the ability of a soldier to complete a visually guided mission. Furthermore, while permanent visual loss associated with distinct morphological damage is of course serious it must also be recognized that temporary shifts in visual acuity or contrast sensitivity can occur at energy densities below those associated with distinct tissue damage. These temporary visual performance shifts could themselves be life threatening and may be the result of reversible or minute physical changes that are undetectable using current damage criteria. Our result suggests that significant shifts in visual sensitivity does occur at or below the ED_{50} level and that these shifts can be long lasting. Using a behavioral technique to measure on-going visual acuity, we have exposed awake, task-oriented rhesus monkeys to a variety of laser exposures which vary in energy density and temporal and spatial distribution on the retina. Our preliminary results in this project are consistent with the results of our previous studies and have extended the various exposure and performance criteria already established.

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PI - Signature 8/30/94 Date

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BACKGROUND

Light induced retinal damage from exposure to field laser sources has potentially serious military implications. Technological advances in the development and employment of laser guided weapons on the modern battlefield has increased the likelihood of exposure. At the same time, lasers being used are becoming more powerful and, due to their brief exposure durations and emitting wavelengths, more difficult to avoid. Standard battlefield lasers are capable of producing serious ocular damage and subsequent disruption of vision. For the soldier, even a temporary visual impairment could jeopardize the individual's ability to complete a visual-motor response and thereby imperil the soldier, fellow soldiers, and overall mission. The establishment of safe operating guidelines for lasers and the development of protective devices where exposures are unavoidable, must remain a high priority of a laser safety program.

Most laser wavelengths currently being employed are transmitted well by the ocular media of the eye and, together with the natural focusing capacity of the eye's optics, produce intense, and often damaging, concentrations of light energy on an extremely absorptive but susceptible retina. The magnitude of ocular damage produced directly depends upon the specific parameters of the exposure condition as well as the absorption characteristics of the tissue irradiated. The site of the damage is somewhat dependent upon the spectral and spatial characteristics of the exposure although for intense, prolonged exposures damage at the optic nerve and receptor level is probable.

Historically, the original studies on the adverse effects of intense irradiation on vision dealt with solar retinitis (1). Since these original and more casual observations, more analytical investigations in the laboratory have focused on the mechanisms of light-induced damage in both the human and infrahuman retina as well as its deleterious impact on visual functioning. The goal of more recent studies has been not only to establish the mechanisms of light insult but also to establish standards for safe viewing in situations when a single exposure is presented. The safety guidelines established have included recommendations for limiting the output power of lasers when situations permit, and for issuing screening goggles for those required to work around high and potentially dangerous levels of light energy. While it is important that any standard established predicts the probability of damage in the single exposure condition, it is of equal concern in today's workplace to be able to predict the outcome of repeated exposures over a prolonged period of time. Individual exposures either of low energy or involving a restricted retinal region may not initially produce any evident visual loss. Repeated exposures to this same region or surrounding areas at similar power densities may eventually accumulate and lead to irreversible morphological damage and significant permanent visual impairments. One of the primary objectives

of the present study is to quantify the cumulative nature of any damage mechanism as well as to elaborate the nature of the transient and permanent visual deficits that might result from a wide variety of exposure conditions simulating those found in the field.

Punctate lesions of the retina resulting from laser irradiation have been extensively investigated from a morphological standpoint. Using suprathreshold dosage levels, gross pathological damage has been reported to occur in the cornea, pigment epithelium and in the outer segments of the photoreceptors (2-5). Several different damage mechanisms have been proposed to explain the observed pathology. Generally, a thermal model has been attributed to those changes resulting from relatively long duration, low energy exposures to long wavelength coherent light, where as mechanical damage mechanisms have typically been associated with extremely high-energy, short duration (Q-switched) pulses. Less frequently, more extensive morphological and behavioral analyses using repeated low energy exposures have shown retinal alterations at power levels well below those where either thermal or mechanical disruptions could be predicted. In these instances, actinic insult has been implicated as the mechanism that produces permanent biochemical changes in the natural cyclic mechanisms within the photoreceptor and which ultimately affect the viability of the receptor cell itself (6, 7). Over the years, as morphological techniques for detecting minimal retinal alterations have been refined, the associated energy densities to produce them have decreased. Associated with these decreases in exposure energy has been a shift in the site of primary anatomical alteration from the pigment epithelial layer to the outer segments of the photoreceptors (8, 9). Since the site of morphological disruption is the location where the initial transduction of light energy to electrochemical energy occurs, it is important to also consider the functional consequences of the induced changes. Examination of these functional changes may not only be a more sensitive measure of subtle changes in retinal morphology and photochemistry but they also relate more closely to the predicted changes in task-related, visual performance that may accompany accidental exposures. Of course, changes in the ability of observers to perform visually following exposure is an important legal issue in cases where medical liability and work disability are pending. It is also of utmost concern to mission planners where successful completion of a mission is dependent upon continued visual and/or visual-motor behavior. It is reasonable to assume that minute enzyme changes in photoreceptors may be associated with single dose exposure levels just below the established ED_{50} or with repetitive low energy exposures and that these subtle changes may not be immediately revealed by more conventional morphological techniques. These rather subtle changes, however, may seriously alter the overall functioning and transmission properties of a photoreceptor and hence disrupt normal visual

sensitivity independent of any obvious structural alterations.

Examination of functional disruptions, especially those immediately following exposure, require a method for accurate placement of the exposure on the fovea. The majority of functional studies to date have employed relatively large diameter and intense power densities which produce not only permanent changes in visual performance, but also severe, irreversible morphological disruptions as well (5, 10, 11, 12). The power levels employed in these studies produced changes in visual acuity ranging from 40 to 80%, the exact amount of deficit reported being directly linked to the amount of foveal-macular tissue exposed (13, 14, 15). Unfortunately, in virtually all previous functional studies dealing with punctate exposures, postexposure measurements of visual performance had to be delayed at least 24 hours because anesthesia was required to properly position the exposure on the fovea. The use of anesthesia eliminated the possibility of determining any dazzle or transient flash effects produced by exposures at power densities at or below the ED_{50} for permanent visual loss. Even for those energy densities significantly above the ED_{50}, it is reasonable to assume that much like morphological damage, the magnitude of the functional alteration may change over time as edema and structural changes occur. Transient changes in optical opacity as a result of hemorrhages, edema and changes in the fine ultrastructure of the retina should have drastic immediate consequences on both fine foveal and coarse peripheral vision. In some missions, the immediate change in one's ability to continue a visually-guided task may be as important a consideration for both the individual and the mission as would be the permanency of these changes. The inability of previous studies to measure the immediate and often transient changes in visual performance following laser exposure has been a serious limitation of these studies in attempting to develop a functional approach to laser safety.

The development of a technique to expose and measure visual acuity in an awake, task-oriented animal was established in the early phases of this effort. This technique not only eliminated the need for anesthesia for placement of exposures on the fovea but also increased the speed of measurement without loss of resolution. The procedure developed requires the animal to maintain central fixation for a prolonged period of time. By aligning a laser beam co-axial with the animal's line of sight, relatively accurate exposure sites can be attained. The development of this procedure was a necessary prerequisite for determining the immediate as well as transient consequences of laser irradiation. A modification of Blough's tracking technique (22) for visual acuity using Landolt rings facilitated rapid measurements of psychophysical thresholds (23, 24). The employment of Landolt rings required the subject to fixate on a predetermined portion of the visual field and for a brief period to maintain

central fixation in order to succeed in the task. This procedure allows accurate placement on the fovea of even very small diameter (50 microns) Q-switched pulses (24).

Visual acuity, the capacity to discriminate an object from the rest of the field of view, has been an important instrument for assessing visual sensitivity following irradiation. Acuity is intermediate in complexity between more simple absolute threshold measures for light detection and more complex form perception. The actual acuity derived is dependent upon a number of factors. Internally, acuity is dependent upon a number of retinal factors including the diameter and distance between photoreceptor outer segments, proportion of unbleached to bleached photopigments present, the clarity of the optical media, and the degree of lateral and convergent neural interconnections, as well as the integrity of physiological mechanisms. Among the more important external factors influencing acuity are the wavelength, intensity, duration, contrast and position of the target within the subject's visual field.

Human experimentation in the area of suprathreshold retinal lesions is virtually impossible since intentional burns can only be performed on eyes that are slated for immediate enucleation. Enucleation is rarely performed on eyes which do not suffer from severe retinopathies in which a substantial loss of vision has already occurred. Furthermore, it is virtually impossible to do a complete functional follow-up on these subjects (16-17). As an alternative, an animal model has been developed with the rhesus as the human prototype. The selection of the rhesus stems from morphological (18 - 21) and functional (20, 23-28) similarities between the two species. While the retinal physiology and presumed visual experiences of humans and monkeys may be quite similar, the cognitive decisions regarding target recognition may be quite different because of differences in reasoning abilities. A possible indication of such differences may come from an analysis of the manner in which these two species adjusted to degraded images either through morphological changes resulting from laser irradiation or through artificial degradation of the target in intact organisms. As part of this effort we have begun to develop a paradigm to explore how humans might respond to targets that have been altered to simulate the type of impairments produced in exposed animals.

METHODS

The behavioral paradigm used for exposing awake, task-oriented animals has been the subject of several research papers (24 - 29). As noted above, this method permits the accurate placement of single, spatially-isolated exposures onto the fovea in an awake, task-oriented animal. In order to simulate field conditions, all exposures were of brief duration (single or multiple Q-switched pulses). Accurate positioning of the exposure onto the fovea is critical for demonstrating a visual acuity deficit. Exposures

outside this region, unless extremely large in diameter, produce little or no acuity deficit since the animal can 'look around" the exposure site(s) and use other, equally or more sensitive, retinal regions to make the required discrimination. Positioning the exposure in the absence of anesthesia was necessary to measure the immediate behavioral consequences of the exposure and to follow any changes in the deficits produced by exposure energies at or near the threshold for permanent damage. Every attempt has been made to make the exposure and assessment paradigms as similar as possible to those conditions under which soldiers might be exposed. In addition, the paradigm has been structured to accommodate the morphological parameters used by others so our data can become part of a larger data base for the establishment of a multi-faceted safety criteria.

<u>Subjects.</u> A colony of six rhesus monkeys has been established for testing under this effort. All animals are males and have normal vision. Some of the animals were present prior to the start of this effort. Two adult animals, acquired under the previous contract, have been replaced. Both were aging primates and had become difficult to handle. One animal who had previously been a well trained subject developed an experimental neurosis and demonstrated stereotypic behaviors that became of concern to our attending veterinarian and to the USDA inspector. This animal's performance became sporadic and at times would cease to press the lever to even the largest of discriminable targets under the highest of avoidance conditions. The other animal was resistant to training for even the simplest of tasks and showed little improvement with practice. Two juveniles were added to the colony as replacements and these animals are in the initial training stages. They have been successfully trained to voluntarily leave the cage and become tractable. Lever training on these animals will begin within the month. Four adult animals have been part of the colony for some time. Each of these animals is tested on a regular basis. One of these animals was exposed to multiple Q-switched pulses of relatively high energy density under a previous effort. This animal's postexposure acuity is tested on a daily basis and his control eye has been exposed under the current effort. A second animal developed an aversion to the paradigm during the period between active projects and during this time demonstrated self-aggressive behavior. Since we have begun again working with this animal, the aversion to handling and testing has decreased significantly along with the self-aggression. Training has continued with some success. Another animal is undergoing baseline acuity testing and should be available for exposure testing in the near future. A fourth animal is trained to press the lever but has not learned the required discrimination; instead the animal is fixated on responding to the discriminable tones rather than visual targets.

The colony of available subjects is limited at any one time to six animals. The animals are maintained according to procedures outlined in the

"Guide and Use of Laboratory Animals" prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources. All animals are males between 1 and 14 years of age and are individually housed in standard primate cages in a climate-controlled room.

Enrichment. Consistent with current USDA regulations (Authority: 7 U.S.C. 2131-2157; 7 CFR 2.17, 2.51, and 371.2g) and federal and local IACUC specifications on primate enrichment, animals are assessed on a daily basis as to their psychological well being and every attempt is made to provide our animals an enriching experience while housed and tested in our laboratory. As required, an enrichment protocol has been established for each animal and a daily record is maintained of the animal's exposure to various enrichment activities. Further, quantitative analyses of the animals' responses to enrichment activities are made to further evaluate the appropriateness of each activity for each animal. Currently enrichment activities include: TV viewing, videotapes of nature scenes, music, food puzzles, play toys, ropes and sticks within the cage, foraging for food, and frequent human interactions. Time budgets have been established for each animal and the animal's caged behavior divided into thirteen different categories:

> Foraging, grooming, inactive, TV Viewing, locomotion, stereotypic, aggressive, sexual, consumption, vocalization, miscellaneous, self aggressive, and feces.

These thirteen behaviors were further divided into two categories described as positive and negative behaviors. The impact of each enrichment activity is assessed in terms of its impact on reducing negative behaviors and increasing the variety and distribution of positive behaviors. A typical example of a time budget for one animal presented with a food puzzle enrichment activity (Figure 1a) and a wooden stick for manipulation (Figure 1b) is shown.

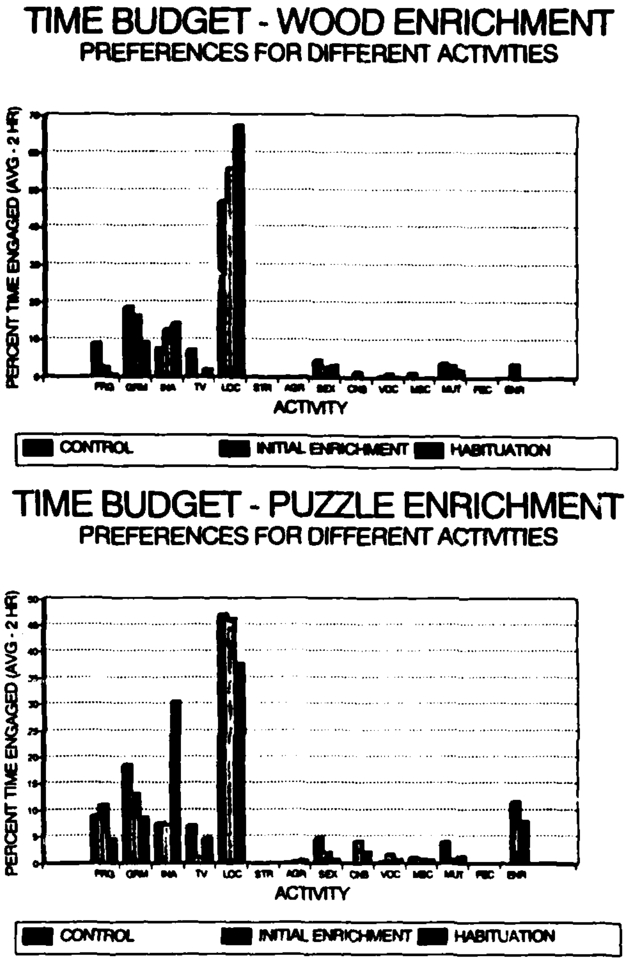
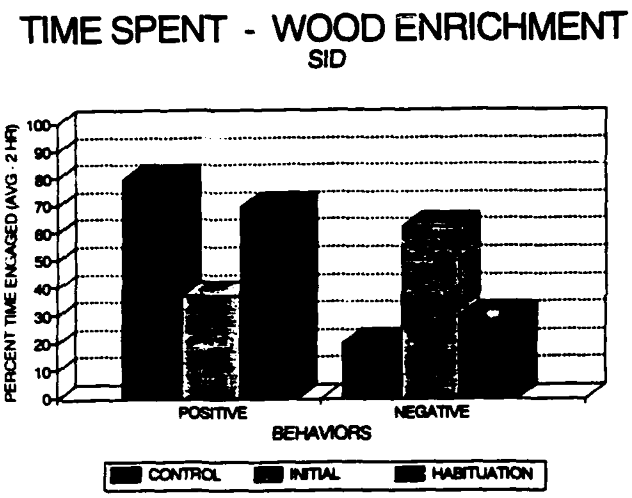
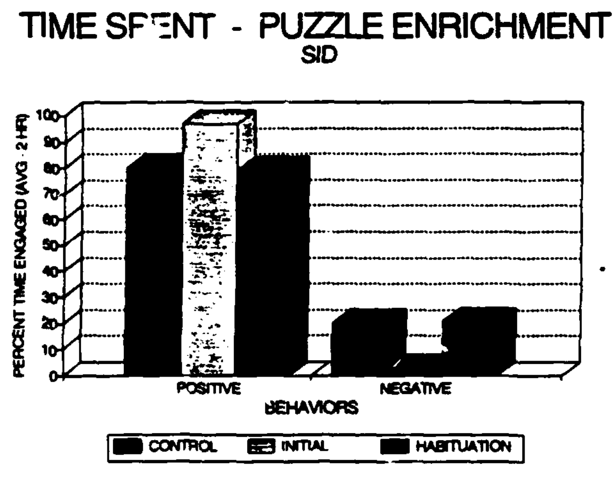


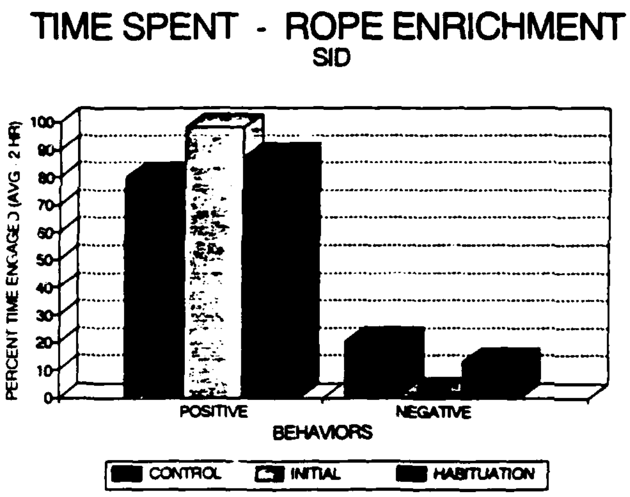
Figure 1. Changes in an animal's activity with the introduction of a wooden pole (a) or food puzzle (b).

Different enrichment activities command different amounts of the animal's attention. Animals also spend more time engaging with the enrichment activity when it is first presented then when it is presented for either a long period of time or

presented on a regular basis. The rate of habituation to each enrichment activity has been measured in terms of its influence on other behaviors, both positive and negative. In Figures 2 -4 the impact of prolonged exposure to wood, rope and food puzzles is shown for one animal. These figures show how the various enrichment activities influence the percent of an animal's time spent in positive (foraging, grooming, locomotion) versus negative (stereotypic, aggressive) behaviors.







Figures 2-4 Impact of different enrichment activities on an animal's ongoing behavior.

Initially, almost every enrichment activity reduced the amount of time the animal spent engaged in what were described as negative behaviors (those representing boredom, stress or maladjustment). Figure 5 demonstrates the relative preference for three different enrichment activities for one animal. This figure demonstrates that, of the three, (rope, puzzle, wood) rope generated the most animal attention and wood the least. These figures also demonstrate that over a relatively short period of time the animals adjust or habituate to each enriching activity no matter how interesting it initially appeared. This data has been interpreted to mean that, regardless of the activity, in order for it to maintain its influence in enriching the animals it must be varied from time to time. The placement of a ball, stick, or even a complex food maze will only momentarily become attractive to the animal. Some activities, like music and TV watching, are varied in themselves so as to maintain some of the

animals attention even if they are presented on a regular cycle.

Apparatus. Animals are tested in a portable restraint apparatus which is used only during the actual test session. At all other times the animals are housed in large primate cages within a primate housing facility. The portable restraint apparatus (see Figure 1) is used to transport the animal to and from the housing colony and to immobilize the animal during testing.

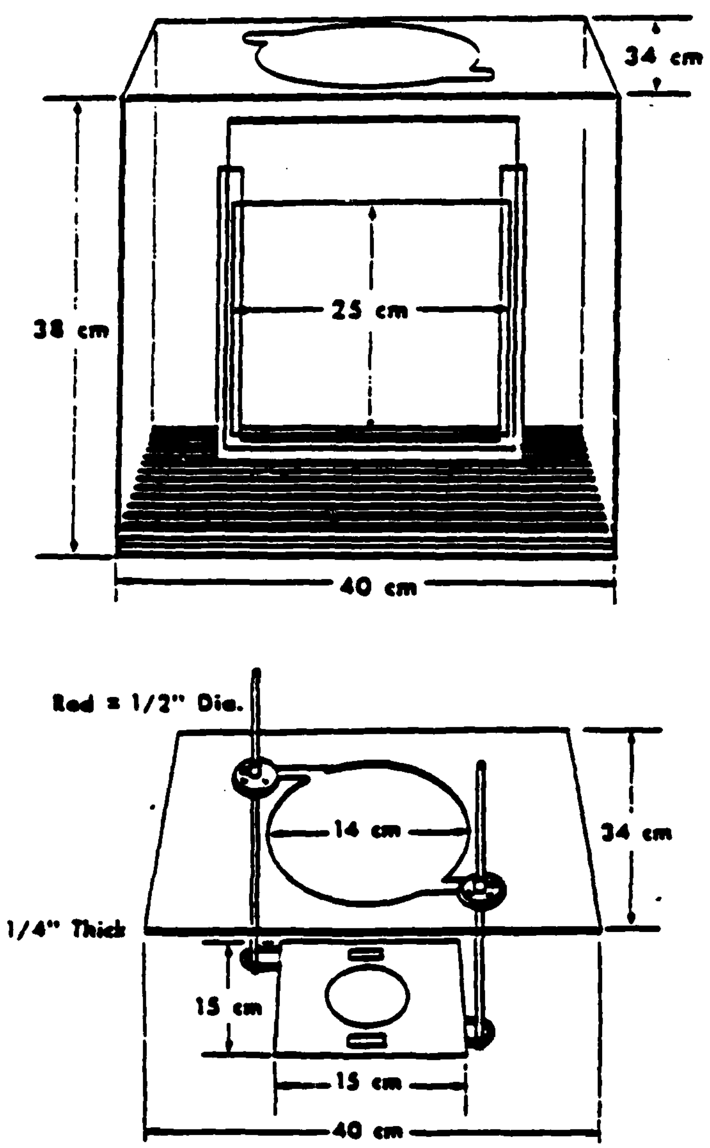


Figure 5. Diagram of the Plexiglas restraint device used to immobilize the animal during transport and testing. A diagram of the collar, worn by the monkey, is shown in the lower diagram. Poles were used to withdrawal the animal's head through the hole in the top of the device and to secure the animal in position.

A custom fitted helmet with an opaque facemask and adjustable iris diaphragm is also used to reduce head and eye movements. This restraint is critical for aligning the animal's pupil with the viewing screen and laser beam. During the course of this project a new customized head restraint was developed using molded plastic and an inner, high density foam liner with an inflatable air bladder to allow for superior stability of the head without undue force or discomfort for the animal. The customized head restraint has openings for the animal's pinnae and a chin strap for reducing vertical head movements.

Animals can be quickly trained to voluntarily leave their home cages and enter the restraint apparatus without resorting to drugs, unnecessary force, or chronic restraint (29). The animals are positively reinforced with Tang and fruit for cooperating. Verbal, facial, and tactile feedback from the animal handler is also an important reinforcing clue. This apparatus is essential for maintaining the animal's line of fixation and distance from the viewing screen which is necessary both for accurate acuity testing and for precise placements of the laser exposure on the retina. All visual acuity measurements are made under monocular conditions, and laser exposures are presented in a Maxwellian view through a 3.0 mm diameter iris diaphragm on the

facemask. Animals are tested in a light-tight, sound attenuated chamber. In the current apparatus, images are projected onto the far wall of the chamber via a rear-projection screen which subtends 4 deg to a distance of 1 m from the subject's pupil. Two programmable carousel slide projectors with coded slide controls are mounted outside the chamber. One of the projectors serves as an image source while the second provides diffuse background luminance when contrast levels are varied. Luminances and wavelengths of the background are controlled by neutral density and interference filters placed in the optical pathway of either projector. Landolt ring targets of different ring diameters are photographically produced on high contrast film. The timing and order for the presentation of these targets is computer controlled by a Cyborg ISAAC A/D interface and IBM 286 microcomputer. The LabSoft software package and Schmitt triggers allow for rapid modifications of incoming and outgoing signals. Data analysis is on-line as well as electronically stored for later call-up and more elaborate analyses. Data can be exported to Lotus or Quattro Pro spreadsheets, analyzed in several on-campus biomedical statistical packages, and graphed on either the screen or printed on a LaserJet or X-Y plotter.

<u>Discrimination</u> <u>Task.</u> Animals are trained to press a lever when they detect the presence of a Landolt ring ("C") randomly positioned within a series of equal-sized completed rings ("0"). Failure to press the lever to the Landolt ring (miss) or pressing the lever during the presentation of a gapless ring (false positive) results in the presentation of a discriminative tone and on a variable reinforcement schedule, a brief, mild electrical shock which varies according to the type of error (miss versus false positive) made. Threshold acuity is derived by a modification of the von Bekesy tracking technique. In this technique, if the subject correctly detects the Landolt ring by pressing a lever, the next series of Landolt rings and gapless rings will be 20% smaller while incorrect detections of the Landolt ring (miss) will produce the presentation of rings 20% larger. The critical feature of the targets (gap in the Landolt "c") can vary from 0.25' to 30' visual angle. Subjects are initially trained to discriminate between Landolt rings and a white light background and gradually converted to detecting the presence of Landolt rings from gapless rings. Due to the payoff matrix used, the number of false alarms is extremely small (<10%) in trained subjects. The dark rings can be presented against backgrounds of different wavelengths and luminances and, with a second diffusing projector, target contrast can be manipulated.

<u>Tracking</u> <u>Eye</u> <u>Movements.</u> A standard corneal eye tracker will be added to the protocol during the next phase of the project. This tracker along with a fundus camera will be supplied by the Army Laser Group at Brooks Air Force Base (formerly the Division of Biorheology at Letterman Army Institute of Research) in accordance with our pre-contract negotiations in the near future.

The eye tracker will be positioned with the test apparatus so as not to interfere with either the viewing screen or laser optical pathway. The eye tracker will be positioned to record the eye movements of the control eye which itself is positioned so as not to have a view of the discriminanda or viewing screen. The output from the eye tracker will be monitored continuously and will be used to assure and verify proper alignment of the laser to a pre-specified position on the animal's retina. Recordings of eye movements will be compared to on-line analyses of the animal's visual performance.

<u>Laser.</u> Two different lasers are currently being used in our laboratory; a 4 W CW Argon laser (Spectra Physics Model 165/265) and a pulsed Nd:YAG laser (Molectron MY 32-20). A small HeNe laser is used for aligning purposes. The lasers are mounted in parallel with each other on an optic bench outside the test chamber. The raw beam from either of the lasers can be selected via movement of a mirror to enter the experimental chamber. The selected laser beam is first directed through several neutral density filters and a manual safety shutter before passing through an electronic shutter and beam splitter. A portion of the attenuated beam from the beam splitter is incident upon a Scientech volume absorbing disc caloriemeter (Model 362) for monitoring output energy. The transmitted portion of the beam is diverted by a 4.5 cm diameter front surface mirror and passes through a 1.25 diopter lens placed 85 cm in front of the animal's pupil. A 5 x 10 cm coated pellicle beam splitter is placed 5 cm in front of the lens and at the intersection of the diverging laser beam and the beam from the viewing screen. The laser beam is positioned such that it is presented to the animal coaxial with a line between the artificial pupil and the gap in a specified, threshold Landolt ring. For determining the line of sight, a 2 mm aperture is placed at the plane of the cornea. A mirror, approximately 2 m behind the 4 mm aperture, is adjusted until it is normal to the line of sight. The beam splitter is then aligned with a coaxial beam from a HeNe laser such that the collimated HeNe beam, along with the Nd:YAG beam, passes through the 4 mm aperture and is reflected off the mirror back onto itself. Coaxial alignments with the line-of-sight are verified by noting that the reflected beam also passes through the 2 mm aperture and back onto the gap in a specified Landolt ring. Calibrations of the energy

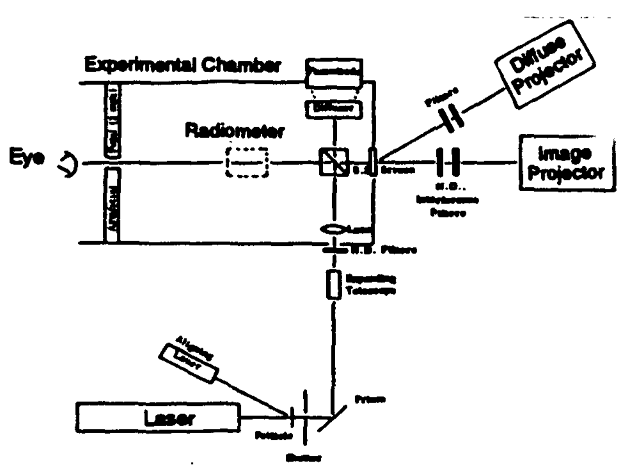


Figure 6. Diagram of the laser and image optical system. The laser beam was presented using a Maxwellian view and coaxial to the gap in a threshold Landolt ring.

density at the cornea and laser head are made by our physicist prior to each exposure according to the method designed by our physicist in collaboration with personnel at Brooks AFB.

<u>Laser Exposure.</u> All exposures are presented to awake animals in the midst of tracking their threshold visual acuity. Especially for exposures below the ED_{50}, a number of different viewing conditions (contrast levels and chromatic backgrounds) are used to assess visual performance prior to and immediately following exposure. Typically, individual exposures are triggered immediately after an animal's correct detection of a pre-determined threshold ring. Observations of animals working under these conditions have shown that they normally maintain fixation on the screen for several seconds following lever pressing. With large diameter spots, this procedure has elicited reliable, immediate shifts in baseline visual acuity over 80% of the time, and presumably reflects foveal involvement. A typical shift in baseline acuity immediately following exposure is shown in Figure 6. In this case the animal's baseline shifted abruptly before gradually returning to the pre-exposure level.

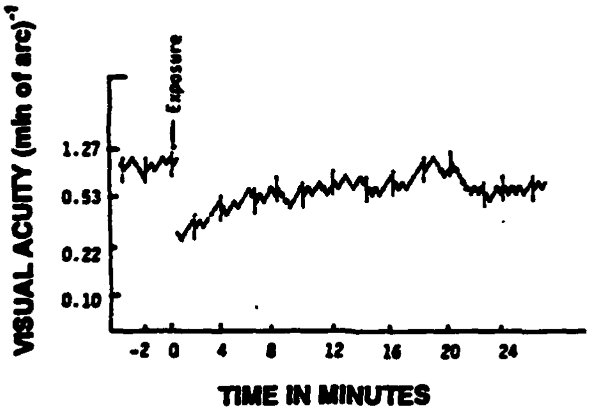


Figure 7. Threshold acuity data following a single, 532 nm, 50 uJ pulse. The vertical lines through the data represent two minute time intervals. Beam diameter on the retina represented less than 50 microns and was presented coaxial with a point on a visual target where the animal was required to maintain fixation.

In cases where no such shifts were obvious, it is presumed that either eye blinking or movement just prior to exposure positioned the beam off-axis and onto the peripheral retina where no obvious deficit in acuity should be noted in our task. Control sessions where no exposures are made, also produced no such shifts in visual acuity and are run periodically. In the near future, an eye tracker device will be modified to following the movements of the control eye during monocular acuity testing in the experimental eye. As this system is perfected, laser exposures will be triggered when pre- specified coordinates from the eye tracker are met.

All animals are exposed to single and repetitive pulses at power levels both significantly above (10, 50 and 100 uJ) and below the ED_{50}. At the present time we have been exposing with only visible (532 nm) light but we will also extend our exposures to include invisible (355 nm and 1064 nm) light. In the multiple pulse mode, animals are presented a train of pulses over a varying time period from less than several milliseconds to greater than several minutes. Spots of various retinal diameters (<50 microns to greater than 800 microns) are presented by varying beam expansion. Exposure wavelengths will include both visible and invisible irradiation from the ND/YAG laser. Pulse repetition rates, beam diameters, and output wavelengths and energies

can be easily manipulated and have been studied in one animal during the early portions of this project at energy levels both above and below the ED_{50}.

A 15 minute baseline acuity assessment precedes each exposure. If the level of pre-exposure performance is within one standard deviation of that previously derived for this animal, then an exposure is made. If not, or if the session variability exceeds baseline variability, the exposure is aborted. Well trained animals routinely return to their past baseline acuity levels and maintain a consistent threshold during this pre-exposure condition. Immediately after exposure, postexposure acuity testing continues until either the animal's acuity recovers or until 30 minutes of time has past, whichever occurs first. If recovery is not complete within the test session, additional daily postexposure measurements are made until the deficit recovers or stabilizes. Following any long term shift in visual acuity, complete contrast and spectral sensitivity curves are derived for both the exposed and control eye. Additional exposures in the experimental or control eye are made following stabilization or recovery of any elicited deficit.

<u>Data analysis.</u> The determination of the animal's performance level and its improvement with time after irradiation is analyzed in accordance with the statistics formulated by Dixon and Massey (1961) for the Up and Down Method. Immediate postexposure acuity is analyzed in two minute blocks of testing using one background condition. Long term deficits are tested daily and mean acuity levels derived until the deficit either stabilizes or recovers. Thresholds for visual acuity are plotted as a function of time following each exposure, and statistical comparisons of these thresholds are made across animals and treatments. Pre- and postexposure spectral and contrast sensitivity functions are derived from all exposures above the ED_{50}.

RESULTS

During the early phase of this effort a significant amount of time was spent in retraining animals previously tested under the preceding contract. A delay in funding and the replacement of our research assistant resulted in a break in our normal daily testing routine. Months of inactivity compounded with a new animal handler created problems for several of our previously well-trained animals. Over time several of these animals underwent significant growth spurts and new head restraints as well as expansions in the restraint box had to be made before the animals could again be tested. In addition, equipment malfunctions and reprogramming of the computer software to accommodate a revised testing routine delayed the onset of the initial training trials. The computer programs are now fully functional, more flexible, and provide more accurate acuity measurements. Our aging laser, which was government supplied for our previous effort, also required extensive repairs. Manufacturer service for this unit is impossible. The original manufacturer as well as

the company which took over the original company are now out of business. Fortunately, a physicist from a nearby military facility, trained in laser calibrations, was identified and he was willing to provide the necessary repairs to place the unit in operation.

The establishment of consistent bar-pressing behavior and discrimination learning was necessary to re-establish each animal's baseline visual sensitivities to various wavelength, luminance, and contrast targets. Re-establishing a consistent baseline was a necessary prerequisite before exposures were made. In addition, several animals were becoming increasingly uncooperative and aggressive partially as a natural part of the aging process. Hazards and increased time associated with handling these animals resulted in their removal from the colony. Due to the short supply of naive and domestic bred animals with certified medical records, only young monkeys were able to be purchased. These animals had to isolated from the colony and allowed to mature to the point where they were large enough to be outfitted in our apparatus.

As we have previously shown, the duration of the initial acuity deficit and the total time for full recovery is directly related to the energy density of the exposure. When relatively small-diameter spot sizes are combined with relatively short exposure durations, as is the case for single Q-switched pulses, it is often difficult to depict any significant change in baseline acuity even when relatively high energy exposures are made. Typically, for the single pulse condition, total recovery time was very rapid, approaching the limit of our procedure to track acuity changes. The transient deficits that were observed were both less in magnitude and shorter in duration than those we have produced using CW lasers of much less total energy. Figure 8 demonstrates the raw data from an animal exposed to a single Nd/YAG pulse which irradiated only a relatively small region of the retina. The data shown in this figure suggests that the animai showed little change in its ability to maintain a consistent, pre-exposure baseline threshold using our up-and-down tracking technique.

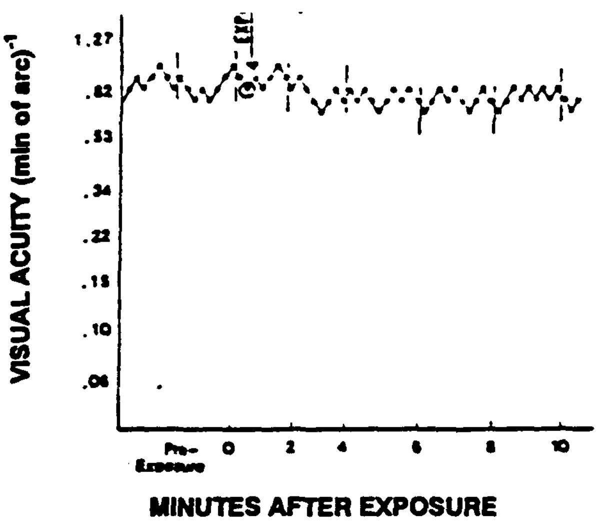


Figure 8. Sample tracking data prior to and immediately following a single, 15 nsec, 10 μJ pulse. This exposure was presented co-axial with the gap in a Landolt ring and produced a spot diameter of less than 50 microns on the retina. The 532 nm pulse was slightly above the projected ED_{50} level for this exposure condition. The vertical lines through the data represent 2 minute time intervals. Each filled circle represents the presentation of a Landolt ring and the vertical lines between the circles represent the presentation of gapless rings of the same ring diameter. The size of test targets are indicated on the ordinate. Each target was presented for approximately 2 seconds and the size of the next series of test targets was contingent upon the animal's correct detection of the Landolt ring within the series of gapless rings.

Increasing the spot diameter or exposing the animal to a series of Q-switched pulses produced a larger initial deficit and, depending upon the total energy of the exposure, a longer recovery time. Figure 9 represents the impact that different spot sizes had on the magnitude of the initial deficit when a single Q-switched pulse is presented. For relatively small diameter spots, only a minimal change in baseline acuity was produced. But as the size of the spot on the retina increased, a larger and larger deficit was elicited consistent with what one would expect as more and more foveal tissue was irradiated. The energy densities used in this example was below those which produced a permanent shift in postexposure visual acuity.

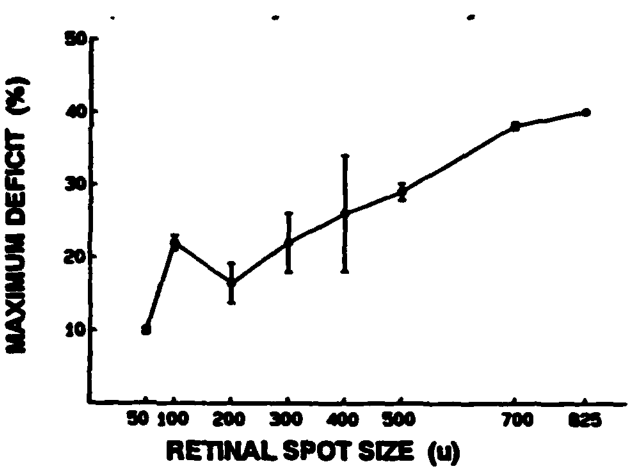


Figure 9. Effects of spot size on the magnitude of the initial deficit. This subject was exposed daily to a single, 3 μJ pulse from a Nd/YAG laser. Each exposure was presented on-axis while the animal was attempting to detect a threshold Landolt ring. Acuity was measured using a high contrast, achromatic target. Each data point represents the mean deficit of several different exposure sessions and the vertical bars represents ± 1 SD.

We have also shown that for longer duration exposures produced by a series of pulse trains, a larger initial deficit can also be produced. Two or more single pulses of equal energy presented in immediate succession produced a greater effect than either exposure alone or one of equal total energy. Separating the single pulses by several minutes or even days also had a larger impact than a single exposure of similar total energy. This suggests not only do eye movements "smear" multiple pulses across a larger retina area, but also there might be some cumulative mechanism operating at the retinal level. In Figure 10 the impact of four separate Q-switched pulses are presented. In this example the animal was exposed to only one pulse per day and for the initial exposures, recovery was complete within 10 to 15 minutes of exposure. However, when exposures were continued recovery was delayed and a point was reached where recovery was no longer possible.

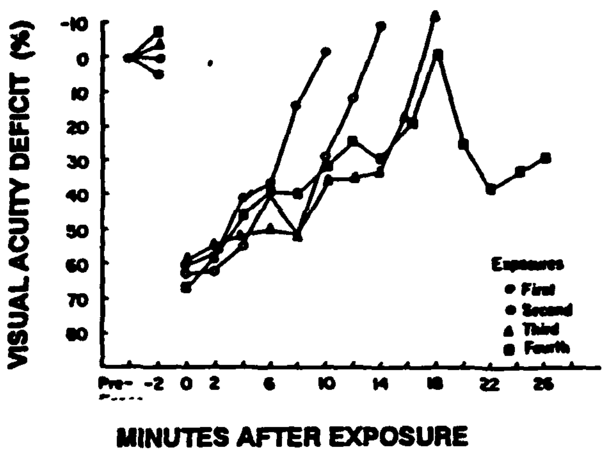


Figure 10. Percent visual acuity deficit following repetitive, 50 μJ, 532 nm pulses. Recovery functions for four different 15 nsec pulses are presented. No more than one exposure was made per day and all exposures were presented coaxial to the gap in a threshold Landolt ring. Acuity was measured under maximum photopic conditions and plotted against the animal's pre-exposure baseline

Changes in the magnitude of the deficits have been shown to be related also to the position of the exposure relative to the fixation point (on- versus off-axis) and to the diameter of the spot on the retina. When the beam is purposely positioned away from the gap in a threshold Landolt ring, the magnitude of the observed deficit is greatly reduced. Positioning the beam outside the region where a foveal exposure might be expected (off-axis) produces little or no shift in visual acuity. In those cases where the laser beam is positioned on-axis (foveal) and where no initial deficit is observed, one might speculate that the animal's point of fixation shifted prior to the presentation of the exposure.

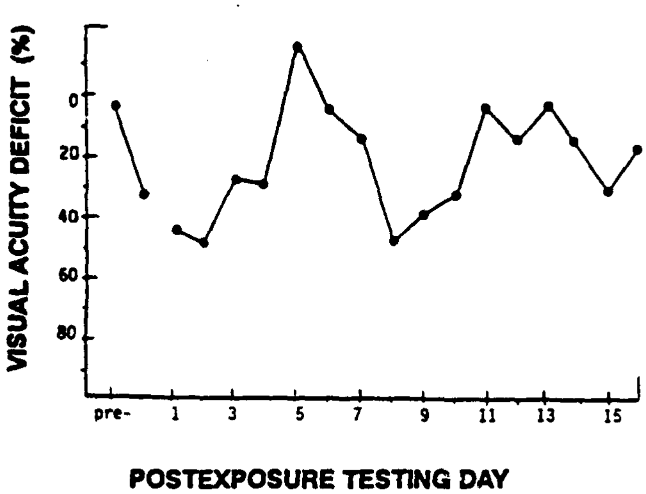


Figure 11. Daily mean postexposure acuity. This animal was exposed to several 50 μJ, 532 nm pulses separated in time by several days. The initial exposures produced only a temporary deficit that appeared to fully recovery during the postexposure testing session. Following several exposures, however, recovery during the test session did not occur and no further laser exposures were made. This figure shows the average of 15 days of postexposure testing. Each data point in this figure represents the average deficit over a 30-45 minute test session.

Postexposure testing following exposure is continued until full recovery is observed. For several animals the initial deficit lasted several days before any significant recovery took place. In some animals the postexposure acuity shifted significantly from day to day (see Figure 11) while in other animals acuity remained consistently depressed over a period of several weeks (see Figure 12).

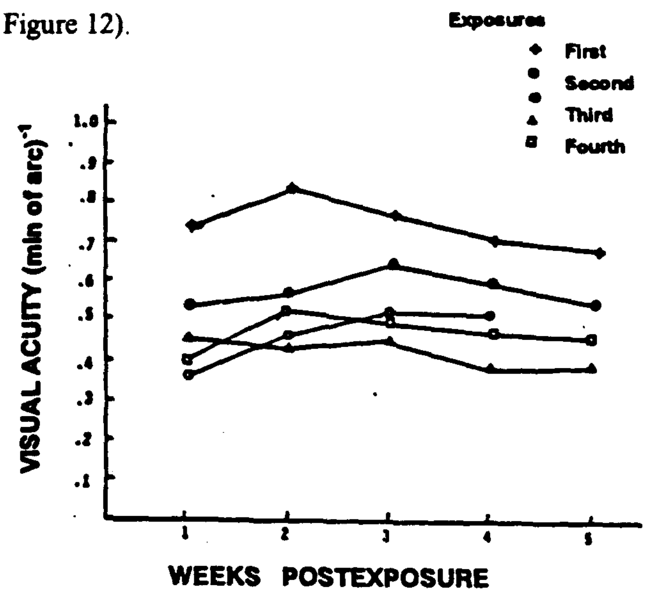


Figure 12. Mean postexposure acuity following four, separate exposures. Each of these curves represent the average daily acuity for the time periods indicated. For example, the uppermost curve represents the weekly postexposure of animal following the first of four single Q-switched laser pulses. Each pulse was 100 μJ and was presented coaxial with the gap in a threshold Landolt ring. Visual acuity was derived under maximum photopic conditions using achromatic targets. Individual exposures were presented at least two months apart from each other.

The postexposure acuity of one animal was followed over a period of several years. The postexposure acuity of the subject presented in Figure 12 has been followed since the animal's last trial of three, 100 μJ pulses. This animal has maintained a rather consistent visual deficit which has not changed significantly over the more than 150 weeks of postexposure testing. Daily mean acuity in the exposed eye has been relatively

consistent as has been this animal's day to day variance. Figure 13 shows this animal's postexposure acuity after two years.

Long Term Acuity in Exposed Eye (OS)

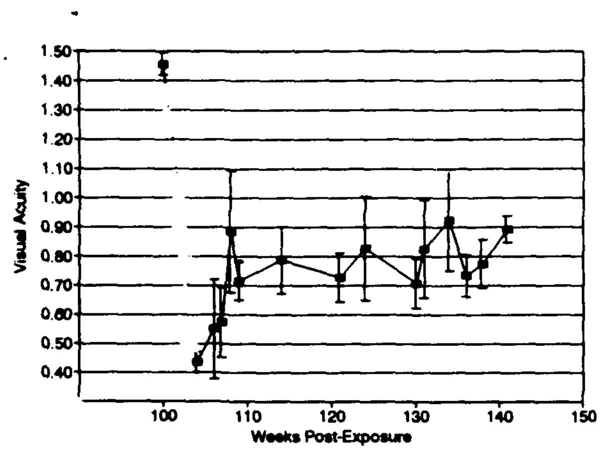


Figure 13. Long term postexposure following four, separate, 100 µJ pulses. Average weekly visual acuity is plotted for a period of approximately one year. The vertical lines represent daily variability. The data points represented mean weekly acuity plotted in terms of visual acuity (min of arc)$^{-1}$.

Spectral Acuity in Exposed Eye (OS)

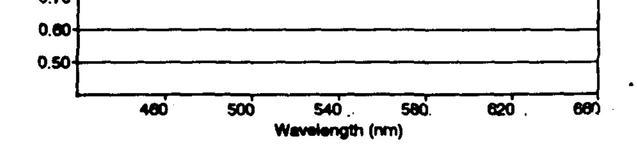


Figure 14. Postexposure spectral acuity. Acuity was measured using different wavelength backgrounds all equated for equal energy. This is the same animal's record as shown in Figure 13 and acuity was measured approximately 2.5 years after the last of three 100 µJ pulse.

DISCUSSION

Although there has been extensive research in this area, there is still much more to be accomplished not only to protect human observers from accidental exposures but also to prevent underutilization of lasers because of unrealistic restrictions placed upon their use. Of particular concern remain the consequences of repetitive pulses, of variations in exposure wavelengths, and of differentiations in the size and position on the retina of the exposure. These issues will be addressed during the second portion of this project. Equally important is a further delineation of the magnitude and duration of elicited losses in visual performance in more complex visual tasks that approximate the type of viewing conditions that are of military relevance. The strategies employed by both nonhuman primates and human subjects to compensate for any real or simulated loss in visual functioning may also have important training significance for the soldier. During the next several months a human subjects protocol will be submitted for local and federal approval . This protocol will establish a means of testing the strategies and outcomes of detection of degraded visual images by normal-sighted human subjects. The images will be degraded to approximate the type visual losses produced in our animal models following laser exposure.

At the onset of this effort, we made several hypotheses which, during the preliminary stages of this effort appear to be supported. First,

light-induced damage to the retina not only disrupts retinal physiology but also function. The type and magnitude of the functional alteration appears related to the location and degree of the retinal insult. Structural damage to photoreceptors should affect an organism's fine resolution capability through changes in the organism's inherent color, brightness, and contrast sensitivities. These changes are especially distinct if foveal areas are involved. Damage to areas outside the fovea may disrupt scotopic and peripheral vision, but are not easily detected unless more complex visual field testing is performed. Using our paradigm, only foveal damage will disrupt photopic acuity although scattered damage throughout the parafoveal region may increase an animals within session variability in our tracking acuity task. Typically we have defined these parafoveal and peripheral exposures as misses; in reality the animal's retina was likely exposed but not in the region where photopic acuity would be altered. We have also observed that the size of the retinal area irradiated affects the magnitude of the observed visual deficit. With small spot sizes, the animal can "look" around the affected regions but as the spot size is increased and more foveal receptors are damaged, an animal's acuity will decrease. Larger spot sizes also increase the probability of a "successful" exposure since they irradiate a larger retinal region and therefore increase the probability that at least some portion of the central fovea might be involved. Exposing the animal to a single pulse (nanoseconds in durations) of relatively small spot diameter (less than 100 microns) evokes only a small lesion even at the highest power densities and therefore produces only minimal acuity loss. Using our acuity task, the animal may use any retinal region to make the required visual discrimination and, if the area is small enough, can still maintain a heightened visual acuity using other, non-exposed foveal areas. Involuntary and voluntary eye movements tend to increase the exposure site when either the pulse duration or number of separate pulses are increased regardless of how small the initial spot diameter may be.

Using a single (15 nsec) pulse of relatively small spot diameter (less than 500 microns) produces little observable photopic acuity deficit. It is likely that at this duration, eye movements produce little "smearing" of the exposure and that, with our voluntary alignment paradigm, the image is not centered precisely within the fovea. Hence at below or near MPE this condition results in no observable acuity deficit in spite of the fact that some temporary or even semi-permanent damage could have occurred. Testing with more spatially complex targets or using more sensitive measures of contrast sensitivity and/or color vision may, in the later portion of this project, increase the probability of detecting minimal shifts in baseline visual performance immediately following exposure.

As previously demonstrated multiple punctate lesions provided by repetitive Q-switched pulses eventually summate to adversely affect any

discrimination requiring the fine resolution capability of the fovea. Fewer, larger diameter lesions should have the same effect as would longer duration, single exposures from a CW laser. Furthermore, repeated exposures of the same retinal region over a period of days or weeks at energy levels below the ED_{50} may increase the susceptibility of that tissue to insult from moderate levels of light irradiation. The time period over which the impact of repetitive exposures may summate may exceed the time for full functional recovery. We have rountinely noted that after several near threshold exposures where there were only minimal baseline shifts elicited, the animal's performance would become more erratic. This increased variability around a previous stable baseline acuity was sometimes temporary, lasting only several days and sometimes more long lasting. This increased variability in visual performance may exist in spite of a sufficient amount of intact foveal tissue to make the required resolution, especially during the early stages following exposure. With time, variability may become reduced and acuity improve as the repair mechanisms proceed, as surrounding unaltered photoreceptors migrate into the area now devoid of active photoreceptors, and/or as the animal improves upon its fixation ability to stabilize the critical features of the target on unexposed portions of the retina.

As we have followed the effects of those exposures which do provide an immediate and sustained deficit in visual acuity some enhancements and decrements in performance over time (days or months) is usually evident. These subtle acuity changes could be explained by an initial edema within or surrounding the exposed tissue that would alter photoreceptor orientation, spacing, and functioning. As a result, the initial deficit would be expected to grow in time, stabilize, and possibly then decrease again depending upon the success of any repair mechanism operating. Hemorrhages within the retina could also result in a temporary clouding of the ocular media thereby increasing light scatter, creating a blurred image, and temporarily reducing the fine resolution capability of the fovea. As the hemorrhage dissipates over time, acuity should again increase. This recovery should be faster than those associated with photoreceptor repair. Also, independent of any transient or permanent morphological change, visual acuity could be disrupted by a dazzle effect from less intense laser exposures. These effects should be immediate and transient and may affect both photopic and scotopic vision. Their time course should correspond to the normal regeneration of pigments but could be longer depending upon any reversible actinic insult that might also accompany the exposure. Psychological variables associated with temporary blindness might also adversely impact the organism's normal foveal fixations and/or the need for fixations outside the central fovea to maximize visual performance. Changes in the ratios of false alarms to correct detection and misses to correct rejections might signal shifts in

the organism's confidence level and strategies employed to complete the task. Ultimately, however, animals in forced-choice tasks where there is a high payoff for performance should develop strategies to maximize their visual performance. Such strategies should involve altered eye movements and points of fixation to facilitate the localization of the critical features of a target on the retinal region with the highest sensitivity. Our data would support the notion that our animals are well trained for the task involved and quickly develop alternative strategies to minimize detection erorrs.

As we change the nature of the discrimination task in future studies the observed loss in visual sensitivity may occur with smaller diameter exposures or fewer repetitive pulses. Spatially distinct, high frequency (resolution), chromatic targets should relate more closely to isolated damage in the fovea than should achromatic targets or those of low spatial resolution which are repeated across the entire visual field. Furthermore, both wavelength and repetition rate of the laser pulses may interact with the type and magnitude of damage elicited, and these two factors should relate directly to changes in visual performance.

With the addition of human subjects in the next portion of this effort we will begin to test the strategies used by motivated subjects to maximize their visual performance. It is anticipated that the strategies employed by human subjects who have no retinal tissue damage but who are viewing degraded visual images will be similar to those observed in our animal studies in retinae that have morphological damage. It should be possible to simulate visual arrays so that they incorporate the type of luminance, color, frequency, and contrast shifts that are associated with real receptor and/or neural loss. Comparison of the eye movements, fixation points, detection rates for various acuity targets, and type of errors encountered in normal-sighted humans for standard versus degraded visual arrays will provide useful information for the development of models to simulate the impact of lasers on vision. Furthermore, it is anticipated that we will be able to differentiate between the type of detection errors committed by motivated subjects viewing degraded images from those subjects who have been encouraged either to become complacent or malinger.

An important new assessment tool to be employed in the continuation of this study is the tracking of eye movements before, during and after laser irradiation. In the past, the position of the eye prior to exposure was predicted based on the animal's visual performance. All laser exposures were made using the assumption that the animal was centrally fixating. In the majority of exposures (80%), an immediate and significant drop in visual acuity was noted which was consistent with what would be expected for a foveal alteration. With the employment of smaller diameter (50 microns) and shorter duration (15 nsec) pulses, the area of involvement within the

fovea for subthreshold flashes is naturally reduced. This has resulted in difficulty in specifying where the exposures may have occurred and in delineating what impact it has on the functioning of that specific area. In this protocol, using an eye tracking device, exposures can be placed on specific areas of the fovea or parafovea and the functions of these areas can be interpreted by assessing any changes in the animal's normal points of central fixation. In addition, the strategies regarding fixation that our highly motivated subjects develop over time may lead to strategies that could be taught to inexperienced human observers who might never have had the need to develop a means of "looking around" an isolated and functionally inoperative retinal area.

The purpose of this study has been to simulate some of the basic parameters of laser exposures that may be encountered in the field and to simulate the type of required visual discriminations that the exposed soldier may need to resolve in order to successfully complete a mission. This study is unique in its ability to generate visual performance data during and immediately following laser exposure allowing the investigators the opportunity to examine threshold shifts at or below the ED_{50}. This information may be of significance in determining how to minimize the area of retinal damage, while at the same time maximizing visual performance during the actual exposure period. The issues associated with ocular damage on the battlefield must extend beyond the medical problem of eye treatment and should include considerations of the successful completion of visually guided missions by those who might be either temporarily or permanently blinded by such irradiation. The functional approach used in the present study directly addresses the issue of changes in visual sensitivities following single and repetitive Q- switched laser pulses, and provides some information as to the type of counter-measures that might be important to consider when developing visual monitors or viewing screens. The immediate consequences of a laser exposure may very well extend beyond simply a discussion of morphological damage and may include discussions of dazzle effect, changes in the fine integration of neural circuits within and across the retina, and any changes in ocular opacity that might result from hemorrhages or tissue movement. Furthermore, this functional approach may be more sensitive to minute enzyme changes within the retina which, like the other changes listed above, can create transient and long term degradations in visual performance similar in magnitude and type to those elicited by distinct morphological damage. The correlation of functional deficits and morphological damage elicited by laser exposures similar to those likely to occur in the field situation is an area that needs further investigation. This study hopefully has partially fulfilled a portion of that need. Furthermore, there is a need to differentiate real visual losses resulting from ocular damage and/or adaptation from fictitious shifts in sensitivity attributed to persons who are malingering. The

next phase of this effort will address the issue of malingering and the development of a behavioral test, based upon performance erro that might be able to differentiate real from fictitious damage. Special attention will be paid to the strategies subjects employed to successfully solve the task. Analyses of response criteria, eye movements, and fixation points may help develop training guidelines that improve mission successes and reduce soldier causalities.

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